44. (Amended) A transgenic mouse cell which comprises at least one endogenous altered LXRα allele that cannot express LXRα that responds to dietary cholesterol.

45. (Amended) The transgenic cell of claim 44, wherein said cell comprises two endogenous altered LXRα alleles that cannot express LXRα that responds to dietary cholesterol.

REMARKS

I. Status of the Claims

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are pending in the application. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. §112, second paragraph for indefiniteness. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. §102(a) over Peet *et al.* The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Applicants note that they previously submitted materials relating to this response on December 13, 2001. However, through an oversight, this response was not submitted at the same time. Thus, applicants request that this response be considered in conjunction with the materials previously submitted.

II. Objections

Claim 11 is objected to. A clarifying amendment is offered.

III. Rejections Under 35 U.S.C. §112

A. Enablement

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are again rejected under the first paragraph of §112 on the grounds that the specification allegedly fails to provide enablement for the full scope thereof. In particular, the examiner argues that claims read on mutations outside LXRα. Applicants traverse, but in the interest of advancing the prosecution, have offered an amendment to all relevant claims stating that the endogenous LXRα gene is "altered," in addition to being unable to respond to dietary cholesterol. It is believed that this amendment addresses the examiner's concerns. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

B. Definiteness

The examiner argues that the phrase "cannot express LXRα sufficient to provide the capacity to respond to dietary cholesterol." Applicants traverse.

The examiner actually parses out two different issues with respect to the above-quoted phrase. First, it is stated that the specification does not identify the ***amount*** of dietary cholesterol involved. The examiner has misunderstood the phrase. As stated at page 58, line 27 of the specification, dietary cholesterol simply refers to that cholesterol provided from exogenous (*i.e.*, diet) sources, as opposed to that cholesterol that is synthesized in the organism (endogenous). Thus, there is no indefiniteness associated with this term as it is used, and the entire discussion of relative amounts (normal, low or high levels) is irrelevant. Rather, the claim simply states that the endogenrous altered LXRα cannot respond to ***any*** dietary cholesterol, *i.e.*, cholesterol above and beyond that produced endogenously.

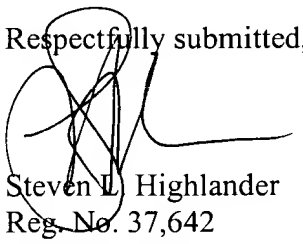
Second, the examiner asks "what specific response or what level of response is contemplated," and "what capacity is being measured." As discussed in the specification, LXRα assists in the clearing and metabolism of cholesterol; in the absence of this function, animals show dramatic hepatic cholesterol accumulation. Again, there is no "level" issue – the alteration in the endogenous LXRα eliminates its ability to metabolize cholesterol. Thus, the claims simply reflect the loss of normal LXRα function due to the alteration. However, in order to clarify the claims, applicants have provided an amendment such that the terms "sufficient" and "capacity" are no longer recited.

Thus, applicants respectfully submit that the pending claims are not indefinite, and are even more clear in their amended form as presented herein. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should Examiner Woitach have any questions regarding this response, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

FULBRIGHT & JAWORSKI, L.L.P.
600 Congress Avenue, Suite 2400
Austin, TX 78701
512-536-3184

Date: January 14, 2003

APPENDIX A - MARKED UP COPY OF CLAIMS

1. (Amended) A transgenic mouse, the cells of which comprise at least one endogenous altered LXRα allele that cannot express LXRα [sufficient to provide the capacity to respond] that responds to dietary cholesterol.

2. (Amended) The transgenic mouse of claim 1, wherein said cells comprise two endogenous altered LXRα alleles that cannot express LXRα [sufficient to provide the capacity to respond] that responds to dietary cholesterol.

4. (Amended) The transgenic mouse of claim 1, wherein a transcript produced from said endogenous altered LXRα allele contains an interruption in the LXRα coding sequence.

5. (Amended) The transgenic mouse of claim 2, wherein a transcript produced from said endogenous altered LXRα alleles both contain an interruption in the LXRα coding sequences.

6. (Amended) The transgenic mouse of claim 1, wherein said endogenous altered LXRα allele contains a nonsense mutation that truncates the corresponding encoded LXRα polypeptide.

7. (Amended) The transgenic mouse of claim 2, wherein said endogenous altered LXRα alleles both contain a nonsense mutation that truncates the corresponding encoded LXRα polypeptide.

8. (Amended) The transgenic mouse of claim 1, wherein said endogenous altered LXRα allele contains a deletion of LXRα coding sequences.

9. (Amended) The transgenic mouse of claim 2, wherein said endogenous altered LXRα alleles both contain a deletion of LXRα coding sequences.

10. (Amended) The transgenic mouse of claim 1, wherein said endogenous altered LXRα allele contains a mutation in the 5' regulatory region of the LXRα gene.

11. (Amended) The transgenic mouse of claim 2, wherein said altered endogenous LXRα alleles both contain a mutation in the 5' regulatory region of the [LXRαs] LXRα genes.

21. (Amended) A method for screening a candidate substance for the ability to reduce cholesterol levels in a mammal comprising:

(a) providing a transgenic mouse, the cells of which comprise at least one endogenous altered LXRα allele that cannot express LXRα [sufficient to provide the capacity to respond] that responds to dietary cholesterol;
(b) treating said mouse with said candidate substance; and
(c) monitoring a cholesterol-related phenotype in said mouse,

wherein a reduction in said cholesterol-related phenotype in said mouse treated with said candidate substance, as compared to a similar mouse not treated with said candidate substance, indicates that said candidate substance reduces cholesterol levels.

26. (Amended) The method of claim 21, wherein said cells comprise two endogenous altered LXRα alleles that cannot express LXRα [sufficient to provide the capacity to respond] that responds to dietary cholesterol.

27. (Amended) A method for screening a candidate substance for the ability to increase bile acid synthesis in a mammal comprising:

(a) providing a transgenic mouse, the cells of which comprise at least one endogenous altered LXRα allele that cannot express LXRα [sufficient to provide the capacity to respond] that responds to dietary cholesterol;
(b) treating said mouse with said candidate substance; and

(c) monitoring a bile acid-related phenotype in said mouse,

wherein an increase in said bile acid-related phenotype in said mouse treated with said candidate substance, as compared to a similar mouse not treated with said candidate substance, indicates that said candidate substance increases bile acid synthesis.

44. (Amended) A transgenic mouse cell which comprises at least one endogenous altered LXRα allele that cannot express LXRα [sufficient to provide the capacity to respond] that responds to dietary cholesterol.

45. (Amended) The transgenic cell of claim 44, wherein said cell comprises two endogenous altered LXRα alleles that cannot express LXRα [sufficient to provide the capacity to respond] that responds to dietary cholesterol.